

EXHIBIT A

Rule 16 Summary of Expert Opinion and Bases

Report date: November 1, 2024

Prepared by: Luli Akinfiresoye, Ph.D.

Substance at issue: *N*-(2-methylphenyl)-*N*-[1-(2-phenylethyl)-4-piperidinyl]propionamide

Alternate name(s): *ortho*-Methylfentanyl; *o*-methylfentanyl

Opinion: Based on a review of the currently available pharmacological data, *ortho*-methylfentanyl has depressant effects on the central nervous system that is similar to the depressant effects on the central nervous system of *N*-(1-phenethylpiperidin-4-yl)-*N*-phenylpropionamide (fentanyl) a Schedule II substance under the Controlled Substances Act (CSA).

Bases and Reasons:

1. Both *ortho*-methylfentanyl and fentanyl are synthetic opioids of the 4-anilidopiperidine structural class. Substances of the 4-anilidopiperidine structural class (e.g., fentanyl) have depressant effect on the central nervous system (CNS).
2. Clinically used opioid analgesics (e.g., fentanyl, morphine, oxycodone etc.) predominantly interact with and activate mu-opioid receptors in the CNS and in other tissues and act as agonists at these receptors.
3. *In vitro* binding and functional studies showed that *ortho*-methylfentanyl, similar to fentanyl, preferentially binds to and activate the mu-opioid receptors (MOR) (DEA-VA, 2024)
 - *ortho*-methylfentanyl and fentanyl's efficacy on mu-opioid receptor activation were evaluated in an *in vitro* MOR activity assay. Data from the study showed that *ortho*-methylfentanyl, similar to fentanyl, act as a mu-opioid receptor agonist.

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4. *In vivo* pharmacological studies have shown that *ortho*-methylfentanyl, similar to fentanyl, has an opioid receptor mediated analgesic effect (DEA-Gatch, 2024).
 - In a warm water tail withdrawal assay, *ortho*-methylfentanyl administered subcutaneously produced analgesic effect as evidenced by dose-dependent increase in tail withdrawal latencies. This analgesic effect of *ortho*-methylfentanyl was attenuated by naltrexone, an opioid receptor antagonist (Gatch, 2024). Thus, *ortho*-methylfentanyl's analgesic effect is mediated by opioid receptor agonism.
 - In the same study, fentanyl when administered subcutaneously was shown to produce analgesic effect in tail-withdrawal test in rodent (Gatch, 2024).
 - Both *ortho*-methylfentanyl and fentanyl were equipotent as analgesics.
5. Abuse of *ortho*-methylfentanyl, similar to fentanyl, has been associated with serious adverse health effects in humans. *ortho*-Methylfentanyl similar to fentanyl, has been positively identified in numerous post-mortem cases (CFSRE, 2024).
6. Based on the above-mentioned pharmacological data, *ortho*-methylfentanyl has a depressant effect on the central nervous system that is similar to the depressant effects of fentanyl, a schedule II substance under the CSA.

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References:

NPS Opioids: Center for Forensic Science and Research Education (CFSRE) (2024)-NPS Opioids in the United States, Quarter 3 Trend Report.

DEA (2024). DEA-VA Interagency Agreement Title: "In Vitro Receptor and Transporter Assays for Abuse Liability Testing for the DEA by the VA" Binding and Functional Activity at Delta, Kappa and Mu Opioid Receptors. (DEA Research Contract).

Gatch MB (2024). *ortho*-methylfentanyl: Test of analgesic effects alone and in combination with naltrexone. 15DDHQ23F00000194, "Evaluation of Abuse Potential of Synthetic Opioids Using In vivo Pharmacological Studies" (DEA Research Contract).

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PROFILE:

- Dr. Akinfiresoye currently serves as a senior pharmacologist with the Diversion Control Division of the Drug Enforcement Administration. Has extensive neuroscience background with excellent administrative, communication, managerial and communication skills in positions of authority,
- Dr. Akinfiresoye has extensive experience in federal governmental contracts and administration, science-based regulatory and policy issues in programs of national prominence,
- Dr. Akinfiresoye evaluates drugs of abuse and other substances for regulatory control under the Federal Controlled Substances Act and provides scientific support to federal, state, and local public health and law enforcement officials related to these substances. Evaluates relevant scientific and drug abuse data on drugs of abuse and provides appropriate advice pertaining to DEA policy and regulation, legislative, and drug scheduling actions related to these drugs.
- Dr. Akinfiresoye is a senior scientific expert in drug addiction and abuse, participating in the international, federal policy and scientific committees and meetings for drug control. Published extensively on peer-reviewed scientific journals, and serving as a scientific expert to review research grants, manuscripts, and testifying at courts.
- Dr. Akinfiresoye served as the Chair of Interagency Committee on Drug Control (ICDC) (08/2021- 02/2023)
 - o The mission of ICDC is a forum where important problem areas in drug control under the Controlled Substances Act and international conventions to support the efforts of heads of member agencies (DEA, FDA, NIDA, and ONDCP) in formulating broad policies for drug control and resolving major questions in coordination of drug scheduling recommendations.
- Dr. Akinfiresoye served as one of the US delegate that participated in discussion on creating the United Nations ToolKit in response to Resolutions of the Commission on Narcotic Drugs which called on UNODC, WHO, INCB and the international community to develop new and innovative approaches to counter the global threats posed synthetic drugs,
- Dr. Akinfiresoye has more than ten years' experience conducting scientific research with specialization in neuroscience, molecular, cellular, and behavioral pharmacology. Conducted research under NIH-funded grants and led neuroscience research team including pre-doctoral and medical student trainees.

KEY EXPERTISE

- Opioid and illicit substance use disorders
- Neuroscience of drug addiction and misuse
- Federal regulatory science and research administration
- US and International drug control.

EDUCATION:

2013- Doctor of Philosophy, Pharmacology, Howard University College of Medicine, Department of Pharmacology, Washington, DC,

2009- Masters of Arts, Clinical Chemistry, University of Scranton, Department of Chemistry Scranton, PA,

2007- Bachelors of Science, Biochemistry, Temple University, Faculty of Arts and Sciences, Philadelphia, PA

PROFESSIONAL EXPERIENCE

Pharmacologist, Drug Enforcement Administration- Diversion Control Division, Drug and Chemical Evaluation Section: December 2015 – Present

Key Project 1

- Provides advisory services in the pharmacology and related biological and physical sciences as applied to the implementation of the Controlled Substances Act (CSA) and recommends, after consideration and evaluation of relevant scientific and drug abuse data, appropriate DEA policy and regulatory, legislative, drug scheduling and other responses relating to the diversion, trafficking and/or abuse of drugs, chemicals and precursors.
- Collects information that defends the DEA's drug control policies to other government agencies, industry, scientific community, domestic drug control bodies and in court proceedings. Assist prosecuting and law enforcement personnel in criminal and regulatory investigations and court proceedings by providing scientific guidance.
- Lead and participate in bilateral data sharing committee for 1): US-DEA- United Nation/WHO Expert Committee on Drug Dependence; 2): US-DEA – Health-Canada Working Group; 3): DEA-NIDA Data Working Group; 4): US- European Monitoring Center for Drugs and Drug Addiction.
- Preparing relevant scientific and technical reviews and regulatory documents of drug control (more than 20 FDA-approved new drugs and non-medical addictive substances) for publication in the Federal Register.

- Coaching and mentoring junior level drug science specialists, pharmacologists, chemists, and program analyst regarding scientific and research topics of pain, drug addiction and control.

Key Projects 2

- Serving as DEA's scientific program officer to lead and coordinate DEA-pharmacological testing program. Evaluating applications, proposals, and adherence to DEA's policies and procedures for research contract applications in the area of behavioral pharmacology (drug addiction and abuse) (\$ 1.65 million funding budgets).
- Providing policy advisement, scientific leadership and administrative coordination for the planning, market research, drafting and execution of initial scientific and technical research proposal [RFI, RFQ or Statement of the Work (SOW) documents, etc.], for collecting data by testing emerging abuse or psychoactive substances including new synthetic opioids, cannabinoids and fentanyl-like drugs for advising science-based drug control policy.
- Serving as a certified FAC-COR II and scientific lead staff, creating and drafting detailed research contract/acquisition plans including project aims, testing options, responsibilities, deliverable schedules, scope, overall costs, oversight/monitoring, contingencies etc.
- Initiating, planning, recommending contract award, managing and performing post-awarded oversight of DEA's research cooperative programs and contracts.
- Performing a variety of management functions associated with the scientific analysis and review of the technical and scientific data generated by research contractors
- Conducting regular virtual or on-site in-person meetings for oversight, monitoring and evaluating the post-award status of progress reporting, with written evaluation summary and progress reports.
- Reviewing and approving scientific findings to direct supporting DEA's mission for science-based drug control policy. Furthermore, the dataset generated from the research programs advances novel knowledge and have contribute to multiple peer-reviewed articles and presentations at prominent scientific conferences.

Other Projects

- Serving as DEA representative official participating in and guiding the activities or as a review committee member of Interagency Committee on Drug Control (including Food and Drug Administration-FDA, NIH, NIDA, Centers for Disease Control and Prevention, The Substance Abuse and Mental Health Services Administration and Office of National Drug Control Policy) and Emerging Opioid Overdose Strategic Group and ensuring continuity in federal approaches toward science-based drug control strategy.

- Serve as pharmacology instructor on emerging drug trends to international partners and the International Law Enforcement Academy.
- Present DEA's research briefings and contracted study findings with the WHO-Expert Committee on Drug Dependence, scientific conferences, or to DEA higher level officials, etc.

Assistant Professor (Adjunct), Northern Virginia Community College, Medical Education Campus: May 2011- present

Summary of duties and responsibilities

- Preparing and leading lectures for pharmacology and medical terminology courses to various health professional students to include pre-med, nursing, emergency responders, respiratory and radiology technology majors through an online course.
- Collaborating with other faculty members on curriculum design, course improvement design.
- Updating and maintain student records and grades.

Scientific Research Program Manager, Howard University College of Medicine, Dept. of Pharmacology: April 2015- December 2015

Summary of duties and responsibilities

- As a program manager, I had established a successful independent innovative research on neurobehavioral diseases using several pre-clinical models focused on mood disorder (depression) and Alzheimer's disease. My research programs were extensively supported by multiple competitively independent research grants from the NIH and other foundation funds.
- Supervised, coached and mentored many junior researchers including 2 pre-doctoral, 3 post-doctoral trainee fellows and 2 technicians, and taught graduate level courses in graduate school and medical, dentistry, and pharmacy schools.
- Collaborated with scientists in the translation of innovative neuroscience research into pre-clinical study design with a major focus on neurobehavioral pharmacology.
- Participated in multi- and transdisciplinary collaborations and in national and professional associations and conferences.

- Planned and monitored team activities versus research project plans and analyzing scientific research gaps.
- Published research findings in original articles in peer-reviewed journals and presented numerous research abstracts on national and international scientific organization meetings, internal and external university seminars, and other venues.

Postdoctoral Fellow, Georgetown University Medical Center, Dept. of Pediatrics: August 2013- March 2015

Summary of duties and responsibilities

- Evaluated the molecular mechanisms underlying the enhancement of P-type Calcium Channel (PTCC) current density in inferior colliculi neurons following alcohol withdrawal.
- Evaluated the extent to which PTCCs contribute to alcohol withdrawal seizure (AWS) generation. This work involved probing the role of R-type calcium channel in epileptogenesis occurrence in neonates exposed to alcohol. Several techniques were used to elucidate the mechanism of action of phosphorylation in the alcohol withdrawal seizure in vivo pharmacological approach combined with molecular genetics and short-interference RNA (siRNA) strategies to determine the extent to which blockade of P-type Ca²⁺ channels using ω -agatoxin TK and anti-CaV2.1a1 subunits siRNA within rat IC suppresses AWS.
- Published research findings in original articles in peer-reviewed journals.
- Developed novel scientific initiatives and stayed current in area of novel research direction through reviews of the relevant literature; educate self about the latest methods and evidence related to innovative research.

Associate Scientist Quality control, Teva Pharmaceuticals: April 2007 – Oct 2007

Summary of duties and responsibilities

- Performed analytical testing of finished dosage pharmaceutical products following analytical methodology.
- Assisted with data audits of standards, reagents, and other analytical instrumentation
- Assisted in ensuring testing was in adherence to schedules cGMP and cGLP requirements

PUBLICATIONS:

1. **Akinfiresoye LR**, Newton J, Suman S, Datta K, N'Gouemo P. Targeted Inhibition of Upregulated Sodium-Calcium Exchanger in Rat Inferior Colliculus Suppresses Alcohol Withdrawal Seizures. *Mol Neurobiology*. 2023.
2. Varshneya NB, Walentiny DM, Stevens DL, Walker TD, **Akinfiresoye LR**, Beardsley PM. Structurally diverse fentanyl analogs yield differential locomotor activities in mice. *Pharmacol Biochem Behav*. 2023.
3. Marusich JA, Gamage TF, Zhang Y, **Akinfiresoye LR**, Wiley JL. In vitro and in vivo pharmacology of nine novel synthetic cannabinoid receptor agonists. *Pharmacol Biochem Behav*. 2022.
4. Varshneya NB, Walentiny DM, Moisa LT, Walker TD, **Akinfiresoye LR**, Beardsley PM. Fentanyl-related substances elicit antinociception and hyperlocomotion in mice via opioid receptors. *Pharmacol Biochem Behav*. 2021.
5. Newton J, **Akinfiresoye LR**, N'Gouemo P. Inhibition of the Sodium Calcium Exchanger Suppresses Alcohol Withdrawal-Induced Seizure Susceptibility. *Brain Sci* 2021.
6. Varshneya NB, Walentiny DM, Moisa LT, Walker TD, **Akinfiresoye LR**, Beardsley PM. Opioid-like antinociceptive and locomotor effects of emerging fentanyl-related substances. *Neuropharmacology* 2019.
7. Newton J, Suman S, **Akinfiresoye LR**, Datta K, Lovinger DM, N'Gouemo P. Alcohol withdrawal upregulates mRNA encoding for Ca v 2.1- α 1 subunit in the rat inferior colliculus. *Alcohol* 2018.
8. **Akinfiresoye LR**, Miranda C, Lovinger DM, N'Gouemo P. Alcohol Withdrawal Increases Protein Kinase A Activity in the Rat Inferior Colliculus. *Alcohol Clin Exp Res*. 2016.
9. P. N'Gouemo, **L. Akinfiresoye**, J. Allard, D. Lovinger. Alcohol withdrawal-induced seizure susceptibility is associated with an upregulation of CaV1.3 channels in the rat inferior colliculus. *The International Journal of Neuropsychopharmacology*, 2015.
10. Yousef Tizabi; Laura L. Hurley; Zakiya Qualls; **Luli Akinfiresoye**. Relevance of the Anti-Inflammatory Properties of Curcumin in Neurodegenerative Diseases and Depression. *Molecules* 2014.
11. Hurley LL, **Akinfiresoye L**, Kalejaiye O, Tizabi Y. Antidepressant Effects of Resveratrol in an Animal Model of Depression. *Brain Behavior Research*, 2014.
12. **Luli Akinfiresoye** and Yousef Tizabi. Antidepressant Effects of AMPA and Ketamine Combination: Role of Hippocampal BDNF, Synapsin and mTOR. *Psychopharmacology*, 2013.

13. Hurley LL, **Akinfiresoye L**, Nwulia E, Kamiya A, Kulkarni AA, Tizabi Y. Antidepressant effect of curcumin in WKY rat model of depression is associated with an increase in hippocampal BDNF. Behav Brain Research, 2012.
14. Tizabi Y, Bhatti BH, Manaye KF, Das JR, **Akinfiresoye L**. Antidepressant-like effects of low ketamine dose is associated with increased hippocampal AMPA/NMDA receptor density in female Wistar-Kyotor rats. Neuroscience, 2012.
15. Gabriel A. Agbor, **Luli Akinfiresoye**, Julianne Sortino, Robert Johnson, Joe A. Vinson. Piper species protect cardiac, hepatic and renal antioxidant status of atherogenic diet fed hamsters. Food Chemistry, 2012.

SELECTED US AND INTERNATIONAL MEETINGS.

- Emerging Trends in Illicit Drug and Production Workshop, The International Law Enforcement Academy, Thailand, Bangkok, May 2023
- Early Warning Systems are Critical to Drug Control Strategies to Protect Public Health and Safety. Lisbon Addictions , Portugal, Lisbon, November 2022
- European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) Expert meeting: 25 years of early warning and response to new psychoactive substances in Europe: past, present, future, Portugal, Cascias, November 2022
- Emerging Trends in Illicit Drug and Production Workshop, The International Law Enforcement Academy, Botswana, Gaborone, March 2022
- Emerging Trends in Illicit Drug and Production Workshop, West Africa Regional Training Center, Ghana, Accra, October 2022
- 'A Peek inside DEA's Process: Drug Scheduling Actions, Pharmacological Testing, and Schedule I Research Registration' mini-symposium, CPDD 2021
- Emerging Trends in Illicit Drug and Production Workshop, The International Law Enforcement Academy, Budapest, Hungary, January 2020